Connecting via Winsock to STN

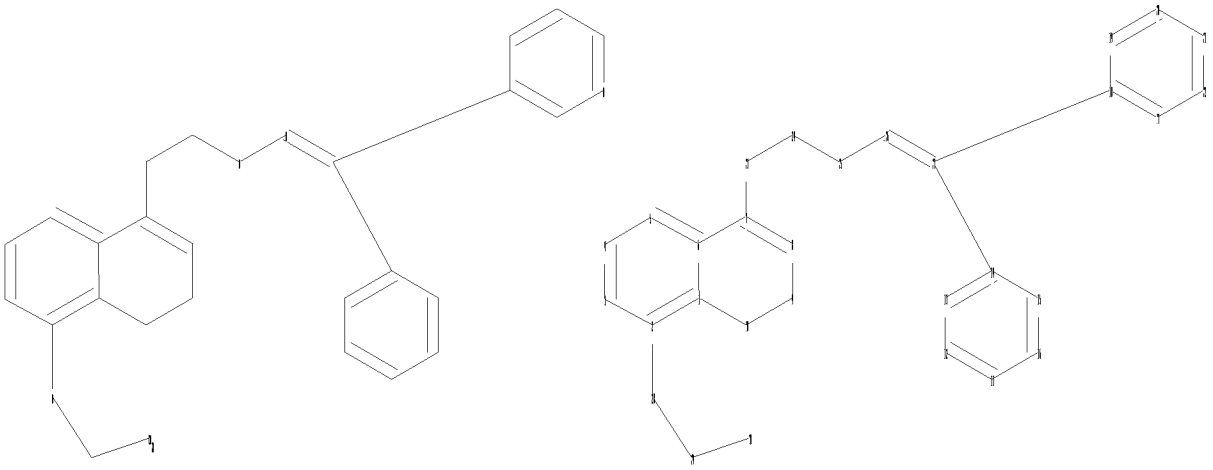
Welcome to STN International! Enter x:x

* * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:23:13 ON 14 APR 2008

=>
=> file reg

=>
Uploading C:\Program Files\Stnexp\Queries\10530685.str



chain nodes :
23 24 25 26 27 28 29 30
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
chain bonds :
2-28 7-23 14-27 18-27 23-24 24-25 25-26 26-27 28-29 29-30
ring bonds :
1-2 1-6 1-10 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 11-12 11-16 12-13 13-14
 14-15 15-16 17-18 17-22 18-19 19-20 20-21 21-22
exact/norm bonds :
2-28 24-25 25-26 26-27 28-29
exact bonds :
1-10 6-7 7-8 7-23 8-9 9-10 14-27 18-27 23-24 29-30

```
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  11-12  11-16  12-13  13-14  14-15  15-16  17-18
17-22  18-19  19-20  20-21  21-22
isolated ring systems :
containing 1 : 11 : 17 :


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:Atom  18:Atom  19:Atom
20:Atom  21:Atom  22:Atom  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS
28:CLASS  29:CLASS  30:CLASS



L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l1 full
L3            4 SEA SSS FUL L1

=> file ca


=> s l2
L4           0 L2

=> d his

     (FILE 'HOME' ENTERED AT 10:23:13 ON 14 APR 2008)

     FILE 'REGISTRY' ENTERED AT 10:23:43 ON 14 APR 2008
L1              STRUCTURE UPLOADED
L2            0 S L1 SAM
L3            4 S L1 FULL

     FILE 'CA' ENTERED AT 10:24:10 ON 14 APR 2008
L4            0 S L2

=> s l3
L5          24 L3

=> d ibib abs fhitstr 1-24

L5   ANSWER 1 OF 24  CA  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        147:268800  CA
TITLE:                   A synthetic small molecule, ONO-1301, enhances
                         endogenous growth factor expression and augments
```

angiogenesis in the ischaemic heart

AUTHOR(S): Nakamura, Kazuto; Sata, Masataka; Iwata, Hiroshi; Sakai, Yoshiki; Hirata, Yasunobu; Kugiyama, Kiyotaka; Nagai, Ryozo

CORPORATE SOURCE: Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan

SOURCE: Clinical Science (2007), 112(11/12), 607-616
CODEN: CSCIAE; ISSN: 0143-5221

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

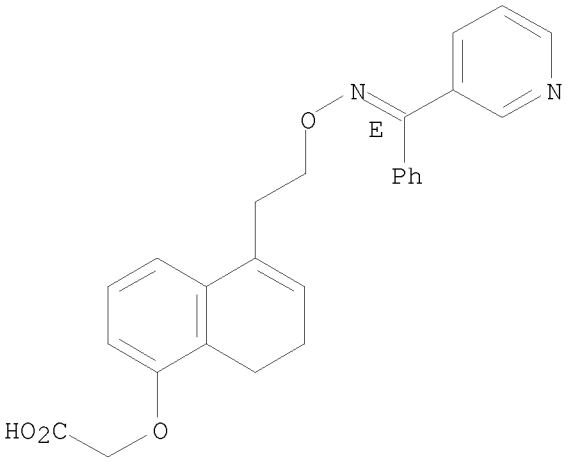
AB It has been shown previously that administration of angiogenic growth factors as genes or proteins can augment collateral growth in ischemic tissues. In the present study, we have investigated the effect of ONO-1301, a synthetic prostacyclin agonist with thromboxane-synthase-inhibitory activity, on expression of endogenous growth factors and angiogenesis. ONO-1301 induced secretion of HGF (hepatocyte growth factor) and VEGF (vascular endothelial growth factor) from cultured normal human dermal fibroblasts in a dose-dependent manner. Dibutyryl cAMP, an analog of cAMP, and forskolin, an adenylate cyclase activator, mimicked the effect of ONO-1301. Conversely, Rp-cAMP (adenosine 3',5'-cyclic monophosphorothioate), an inhibitor of cAMP, partially inhibited the effect of ONO-1301, suggesting that cAMP mediated the effect of ONO-1301 in up-regulating the expression of HGF and VEGF, at least in part. ONO-1301 promoted tube-like formation by HUVECs (human umbilical vein endothelial cells) when co-cultured with fibroblasts, and the angiogenic effect of ONO-1301 was abrogated by administration of a neutralizing antibody against HGF or VEGF. To generate a slow-releasing form of ONO-1301, ONO-1301 was mixed with poly(DL-lactic-co-glycolic acid). The slow-releasing form of ONO-1301 was injected directly into the ischemic myocardium of mice immediately after ligation of the left anterior descending artery. The slow-releasing form of ONO-1301 up-regulated HGF and VEGF expression and increased capillary d. in the border zone (342.7±29.7 capillaries/mm2 in controls compared with 557.2±26.7 capillaries/mm2 in treated animals; $P < 0.01$) at 7 days. The slow-releasing form of ONO-1301 ameliorated left ventricular enlargement after 28 days and improved survival rate. In conclusion, our results indicate that ONO-1301 up-regulated endogenous growth factors and promoted angiogenesis in response to acute ischemia. Therefore ONO-1301 might have a therapeutic potential in treating ischemic diseases.

IT 176391-41-6, ONO-1301
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ONO-1301 enhances endogenous growth factor expression and augments angiogenesis in ischemic heart)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 145:159839 CA
TITLE: GLP-1 production enhancers containing prostaglandin receptor agonists
INVENTOR(S): Sakai, Yoshinori
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 34 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2006199694	A	20060803	JP 2005-369929	20051222
PRIORITY APPLN. INFO.:			JP 2004-374462 A	20041224

OTHER SOURCE(S): MARPAT 145:159839

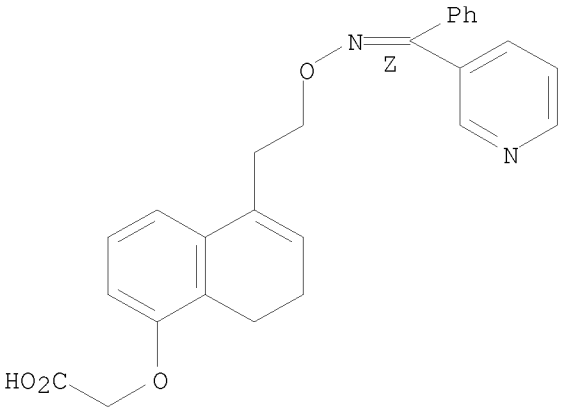
AB The invention provides a GLP-1 (glucagon-like peptide-1) production enhancer containing prostaglandine receptor agonist, especially, IP agonists, wherein the agent is suitable for use for treatment of diabetes, hyperlipidemia, and diabetic complication. A pharmaceutical composition containing the GLP-1 production enhancer and another active component is also disclosed. For example, the effect of (E)-[5-[2-[1-phenyl-1-(3-pyridyl)methylideneaminooxy]ethyl]-7,8-dihydronaphthalen-1-yloxy]acetic acid (I) on blood glucose in KK-Ay/Ta Jcl mice was examined Also, a tablet containing I 5 mg was formulated.

IT 153814-74-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GLP-1 production enhancers containing prostaglandin receptor agonists)

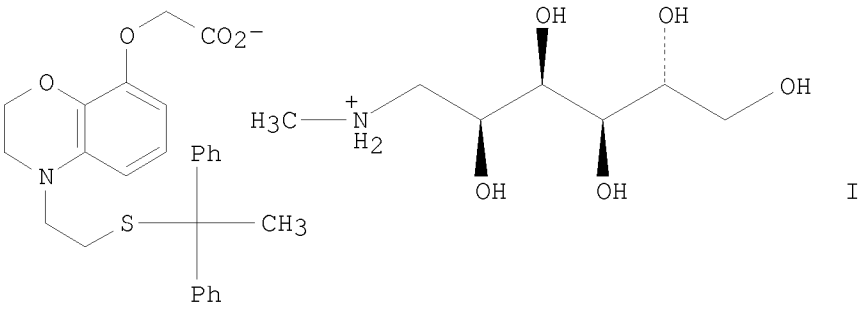
RN 153814-74-5 CA
CN Acetic acid, [[7,8-dihydro-5-[2-[[(Z)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (9CI) (CA INDEX

NAME)

Double bond geometry as shown.



L5 ANSWER 3 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:343062 CA
TITLE: Development of 3,4-dihydro-2H-benzo[1,4]oxazine derivatives as dual thromboxane A2 receptor antagonists and prostacyclin receptor agonists
AUTHOR(S): Ohno, Michihiro; Tanaka, Yoichiro; Miyamoto, Mitsuko; Takeda, Takahiro; Hoshi, Kazuhiro; Yamada, Naohiro; Ohtake, Atsushi
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Toray Industries, Inc., Kamakura, Kanagawa, 248-8555, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2006), 14(6), 2005-2021
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:343062
GI



I

AB We discovered a novel series of 3,4-dihydro-2H-benzo[1,4]oxazin-8-yloxyacetic acid derivs. as potent dual-acting agents to block the TXA2

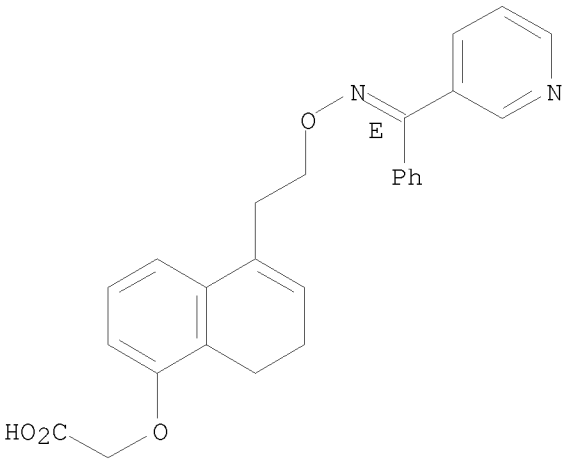
receptor and to activate the PGI2 receptor. We report the synthesis, structure-activity relationship, and in vitro, ex vivo, and in vivo pharmacol. of this series of compds. 4-[2-(1,1-Diphenylethylsulfanyl)ethyl]-3,4-dihydro-2H-benzo[1,4]oxazin-8-yloxyacetic acid N-methyl--glucamine salt (7)(I) is a promising candidate for a novel treatment in the anti-thrombotic and the cardiovascular fields avoiding hypotensive side effects.

IT 176391-41-6, ONO-1301
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Development of 2H-benzoxazine derivs. as dual thromboxane A2 receptor antagonists and prostacyclin receptor)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 144:324510 CA

TITLE: Non-prostanoid prostacyclin agonists for the treatment of pulmonary arterial hypertension

AUTHOR(S): Antoniu, Sabina A.

CORPORATE SOURCE: Clinic of Pulmonary Disease, Iasi, 700115, Rom.

SOURCE: Expert Opinion on Investigational Drugs (2006), 15(3), 327-330
CODEN: EOIDER; ISSN: 1354-3784

PUBLISHER: Ashley Publications Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pulmonary arterial hypertension (PAH) is a rare disease with various causes. Vasoconstriction, in situ thrombosis and thickening of the smaller pulmonary artery walls leads to an increase in pulmonary artery pressure, right heart failure and eventually death. Currently, several specific therapies are available for PAH treatment, including sildenafil citrate, bosentan, epoprostenol and prostanoid derivs. ONO-1301 is a

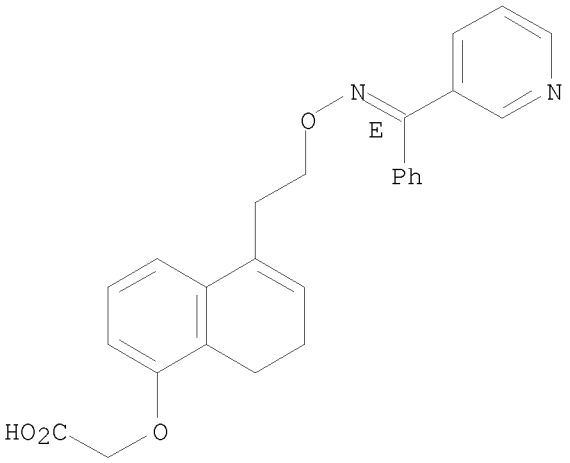
long-acting non-prostanoid prostacyclin agonist, which is currently in development for several conditions including PAH. This is a proof-of-concept study demonstrating antiremodelling and -thrombotic activity and vasodilatory properties of ONO-1301 in monocrotaline-induced PAH rat model.

IT 176391-41-6, ONO-1301
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-prostanoid prostacyclin agonists for the treatment of pulmonary arterial hypertension)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 144:267014 CA

TITLE: Prostacyclin agonist with thromboxane synthase inhibitory activity (ONO-1301) attenuates bleomycin-induced pulmonary fibrosis in mice

AUTHOR(S): Murakami, Shinsuke; Nagaya, Noritoshi; Itoh, Takefumi; Kataoka, Masaharu; Iwase, Takashi; Horio, Takeshi; Miyahara, Yoshinori; Sakai, Yoshiki; Kangawa, Kenji; Kimura, Hiroshi

CORPORATE SOURCE: Department of Regenerative Medicine and Tissue Engineering, National Cardiovascular Center Research Institute, Osaka, Japan

SOURCE: American Journal of Physiology (2006), 290(1, Pt. 1), L59-L65
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The balance between prostacyclin and thromboxane A2 (TXA2) plays an important role in pulmonary homeostasis. However, little information is

available regarding the therapeutic potency of these prostanoids for pulmonary fibrosis. The authors have recently developed ONO-1301, a novel long-acting prostacyclin agonist with thromboxane synthase inhibitory activity. Thus the authors investigated whether repeated administration of ONO-1301 attenuates bleomycin-induced pulmonary fibrosis in mice. After intratracheal injection of bleomycin or saline, mice were randomized to receive repeated s.c. administration of ONO-1301 or vehicle. Bronchoalveolar lavage (BAL) and histol. analyses were performed at 3, 7, and 14 days after bleomycin injection. In vitro studies using mouse lung fibroblasts were also performed. ONO-1301 significantly attenuated the development of bleomycin-induced pulmonary fibrosis, as indicated by significant decreases in Ashcroft score and lung hydroxyproline content. ONO-1301 significantly reduced total cell count, neutrophil count, and total protein level in BAL fluid in association with a marked reduction of TXB2.

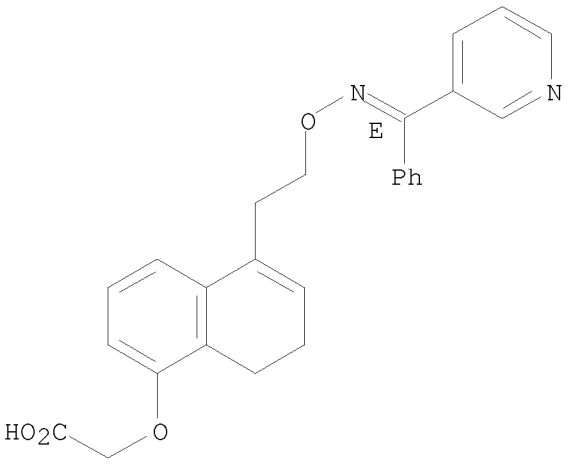
A single administration of ONO-1301 significantly increased plasma cAMP level for >2 h. In vitro, ONO-1301 and a cAMP analog dose-dependently reduced cell proliferation in mouse lung fibroblasts. The reduction in cell proliferation by ONO-1301 was attenuated by a protein kinase A (PKA) inhibitor. Furthermore, bleomycin mice treated with ONO-1301 had a significantly higher survival rate than those given vehicle. These results suggest that repeated administration of ONO-1301 attenuates the development of bleomycin-induced pulmonary fibrosis and improves survival in bleomycin mice, at least in part by inhibition of TXA2 synthesis and activation of the cAMP/PKA pathway.

IT 176391-41-6, ONO-1301
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostacyclin agonist with thromboxane synthase inhibitory activity (ONO-1301) attenuates bleomycin-induced pulmonary fibrosis in mice and mechanisms involved)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



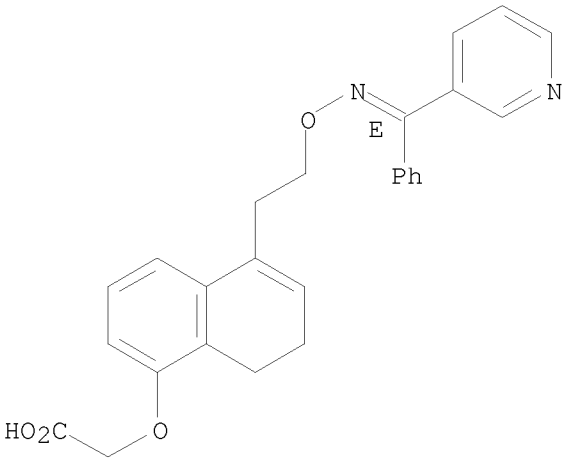
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:442242 CA
TITLE: Prostacyclin attenuates oxidative damage of myocytes by opening mitochondrial ATP-sensitive K+ channels via the EP3 receptor
AUTHOR(S): Shinmura, Ken; Tamaki, Kayoko; Sato, Toshiaki; Ishida, Hideyuki; Bolli, Roberto
CORPORATE SOURCE: Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
SOURCE: American Journal of Physiology (2005), 288(5, Pt. 2), H2093-H2101
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prostacyclin (PGI2) and the PGE family alleviate myocardial ischemia-reperfusion injury and limit oxidative damage. The cardioprotective effects of PGI2 have been traditionally ascribed to activation of IP receptors. Recent advances in prostanoid research have revealed that PGI2 can bind not only to IP, but also to EP, receptors, suggesting cross talk between PGI2 and PGEs. The mechanism(s) whereby PGI2 protects myocytes from oxidative damage and the specific receptors involved remain unknown. Thus fresh isolated adult rat myocytes were exposed to 200 μM H2O2 with or without carbaprostacyclin (cPGI2), IP-selective agonists, and ONO-AE-248 (an EP3-selective agonist). Cell viability was assessed by trypan blue exclusion after 30 min of H2O2 superfusion. ONO-AE-248 and cPGI2 significantly improved cell survival during H2O2 superfusion; IP-selective agonists did not. The protective effect of cPGI2 and ONO-AE-248 was completely abrogated by pretreatment with 5-hydroxydecanoate or glibenclamide. In the second series of expts., the mitochondrial ATP-sensitive K+ (KATP) channel opener diazoxide (Dx) reversibly oxidized flavoproteins in control myocytes. Exposure to prostanoid analogs alone had no effect on flavoprotein fluorescence. A second application of Dx in the presence of cPGI2 or ONO-AE-248 significantly increased flavoprotein fluorescence compared with Dx alone, but IP-selective agonists did not. This study demonstrates that PGI2 analogs protect cardiac myocytes from oxidative stress mainly via activation of EP3. The data also indicate that activation of EP3 receptors primes the opening of mitochondrial KATP channels and that this mechanism is essential for EP3-dependent protection.

IT 176391-41-6, ONO-1301
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(prostacyclin attenuation of oxidative damage of rat cardiomyocytes by opening mitochondrial ATP-sensitive potassium channels via EP3 receptors)
RN 176391-41-6 CA
CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:404678 CA
TITLE: Differential effect of prostaglandins E1 and E2 on lipopolysaccharide-induced adhesion molecule expression on human monocytes
AUTHOR(S): Takahashi, Hideo K.; Iwagaki, Hiromi; Tamura, Ryuji; Katsuno, Goutaro; Xue, Dong; Sugita, Sachi; Mori, Shuji; Yoshino, Tadashi; Tanaka, Noriaki; Nishibori, Masahiro
CORPORATE SOURCE: Department of Pharmacology, Okayama University Graduate School of Medicine and Dentistry, 2-5-1 Shikata-cho, Okayama, 700-8558, Japan
SOURCE: European Journal of Pharmacology (2005), 512(2-3), 223-230
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of prostaglandins E1 and E2 on the 1 ng/mL lipopolysaccharide-induced expression of intercellular adhesion mol. (ICAM)-1, B7.1, B7.2, CD40 and CD40 ligand (CD40L) on monocytes was examined Prostaglandin E1 suppressed B7.1 and CD40 expression, but prostaglandin E2 did not effect on any type of adhesion mol. expression. Both prostaglandins inhibited tumor necrosis factor (TNF)-α production and T-cell proliferation of lipopolysaccharide-treated human peripheral blood mononuclear cells (PBMC). Among prostaglandin E1 receptors (IP/EP1/EP2/EP3/EP4) agonists, ONO-1301, a prostanoid IP-receptor agonist, prevented B7.1 and CD40 expression. ONO-AE1-259-01 a prostanoid EP2-receptor agonist, ONO-AE1-329, a prostanoid EP4-receptor agonist, and ONO-1301 inhibited TNF-α production and T-cell proliferation. Moreover, anti-B7.1 and anti-CD40 Abs prevented lipopolysaccharide-induced TNF-α production and T-cell proliferation. Therefore, the effect of prostaglandin E1 on TNF-α production and T-cell proliferation might depend on the inhibition of B7.1 and CD40 expression, but that of prostaglandin E2 might be independent of adhesion mols. expression. In conclusion, the mechanism

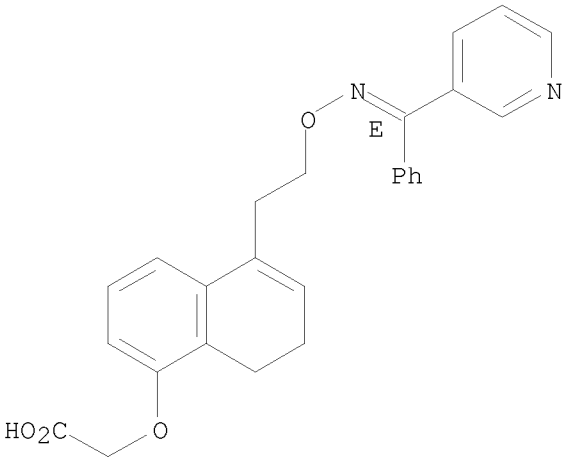
responsible for the effect of prostaglandin E1 on lipopolysaccharide-induced responses is distinct from that of prostaglandin E2.

IT 176391-41-6, ONO-1301
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(PGE1 and PGE2 differential effect on lipopolysaccharide-induced adhesion mol. expression on human monocytes and mechanism therein)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 141:388381 CA

TITLE: TRA-418, a novel compound having both thromboxane A2 receptor antagonistic and prostaglandin I2 receptor agonistic activities: Its antiplatelet effects in human and animal platelets

AUTHOR(S): Yamada, N.; Miyamoto, M.; Isogaya, M.; Suzuki, M.; Ikezawa, S.; Ohno, M.; Otake, A.; Umemura, K.

CORPORATE SOURCE: Clinical Development Center, Toray Industries, Inc., Chiba, Japan

SOURCE: Journal of Thrombosis and Haemostasis (2003), 1(8), 1813-1819
CODEN: JTHOA5; ISSN: 1538-7933

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB TRA-418 is a novel compound that has been found in our screening for compds. having both thromboxane A2 (TP) receptor antagonistic and prostaglandin I2 (IP) receptor agonistic activities. In the binding assays, TRA-418 showed a 10-fold higher affinity to TP-receptors than IP-receptors. TRA-418 inhibited platelet aggregation induced by the TP-receptor agonist, U-46619 and by arachidonic acid at concns. lower than those required for inhibition of ADP-induced aggregations. Furthermore, TRA-418 inhibited

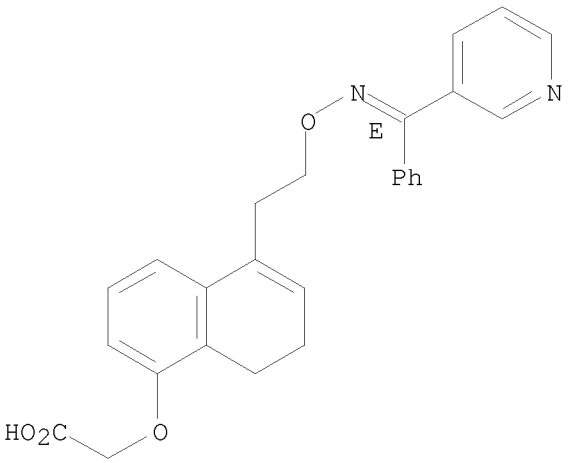
not only platelet aggregation induced by ADP alone, but also that induced by ADP in the presence of the TP-receptor antagonist, SQ-29548. When the IC50 values of TRA-418 for platelet aggregation were estimated in platelet prepns. from monkeys, dogs, cats, and rats using ADP and arachidonic acid as the platelet stimulating agents, it was found that the values estimated in monkey platelets were quite similar to those estimated in human platelets. In ex vivo platelet aggregation in monkeys, TRA-418 exhibited significant inhibitory effects on arachidonic acid-induced aggregation in platelet prepns. from monkeys treated at 3 μg kg min-1 or higher doses, where neither a significant decrease in blood pressure nor a significant increase in heart rate was observed These results are consistent with the fact that TRA-418 has a relatively potent TP-receptor antagonistic activity together with a relatively weak IP-receptor agonistic activity.

IT 176391-41-6, ONO-1301
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IP-receptor agonist ONO-1301 inhibited platelet aggregation induced by any of platelet stimulating agents except for arachidonic acid in presence of epinephrine in human PRP)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:344926 CA
TITLE: Endogenous repair factor production promoters containing PGI2, EP2, or EP4 agonists
INVENTOR(S): Sakai, Yoshiki; Nishiura, Akio; Ogata, Teppei
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004032965	A1	20040422	WO 2003-JP12981	20031009
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003272963	A1	20040504	AU 2003-272963	20031009
EP 1563846	A1	20050817	EP 2003-754060	20031009
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 20060069018	A1	20060330	US 2005-530685	20050408

PRIORITY APPLN. INFO.:	JP 2002-298079	A	20021010
	JP 2002-318830	A	20021031
	JP 2003-117604	A	20030422
	JP 2002-318820	A	20021031
	WO 2003-JP12981	W	20031009

OTHER SOURCE(S): MARPAT 140:344926

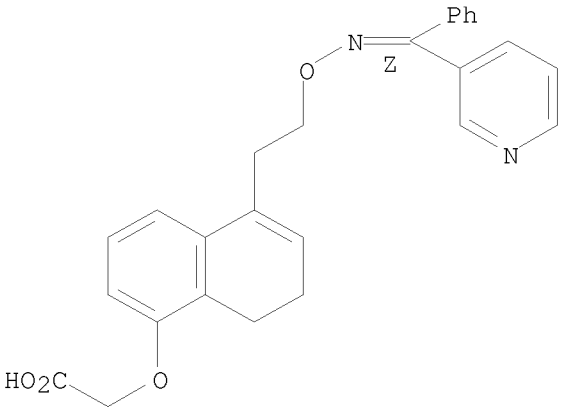
AB Disclosed are promoters for the production of endogenous repair factors containing one or more members selected from among prostaglandin (PG) I2 agonist, EP2 agonist and EP4 agonist. Because of being capable of promoting the production of various endogenous repair factors and having effects of promoting angiogenesis and inducing stem cell differentiation, prostaglandin (PG) I2 agonist, EP2 agonist and EP4 agonist are useful in preventing and treating ischemic organ failures (arteriosclerosis obliterans, Buerger's disease, Raynaud's disease, myocardial infarction, angina, diabetic neuropathy, vertebral stenosis, cerebrovascular disorders, brain infarction, pulmonary hypertension, bone fracture, Alzheimer's disease, etc.). A sustained release microsphere containing a PGI2 agonist (E)-[5-[2-[1-phenyl-1-(3-pyridyl)methylidyne aminooxy]ethyl]-7,8-dihydronaphthalen-1-yloxy]acetic acid (I) was prepared with polylactic acid-glycolic acid copolymer. The microsphere was administered to obstructive arteriosclerosis model rats by intrmuscluar injection to examine the effect of I on angiogenesis.

IT 153814-74-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endogenous repair factor production promoters containing PGI2, EP2, or EP4 agonists)

RN 153814-74-5 CA

CN Acetic acid, [[7,8-dihydro-5-[2-[[(Z)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:123097 CA
TITLE: Unique regulation profile of prostaglandin E1 on adhesion molecule expression and cytokine production in human peripheral blood mononuclear cells
AUTHOR(S): Takahashi, Hideo Kohka; Iwagaki, Hiromi; Tamura, Ryuji; Xue, Dong; Sano, Masahiro; Mori, Shuji; Yoshino, Tadashi; Tanaka, Noriaki; Nishibori, Masahiro
CORPORATE SOURCE: Department of Pharmacology, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 307(3), 1188-1195
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, the authors examined the effects of prostaglandin E1 (PGE1) on the expression of intercellular adhesion mol. (ICAM)-1, B7.1, B7.2, CD40, and CD40 ligand (CD40L) on peripheral blood mononuclear cells (PBMC) using fluorescence-activated cell sorting anal. as well as its effects on cytokine production using ELISA. Whereas no inhibitor of spontaneous expression of adhesion mols. was reported, the authors found that PGE1 inhibited spontaneous ICAM-1, B7.2, and CD40 expression on monocytes in a concentration-dependent manner but had no effect on the expression of B7.1 and CD40L. Although interleukin (IL)-18 induced the expression of ICAM-1, B7.2, CD40, and CD40L, PGE1 prevented IL-18-induced expression of ICAM-1, B7.2, and CD40. The authors examined the involvement of five subtypes of PGE1 receptors (IP, EP1, EP2, EP3, and EP4) in the effect of PGE1 on the expression of these adhesion mols. using subtype-specific agonists. Among EP receptor agonists, EP2 and EP4 receptor agonists inhibited IL-18-elicited ICAM-1, B7.2, and CD40 expression. ONO-1301 (IP receptor agonist) prevented the expression of ICAM-1, B7.2, and CD40 regardless of the presence of IL-18 with the same potency as PGE1. The effect of a combination of ONO-1301 and 11-deoxy (D)-PGE1 (EP2/EP4

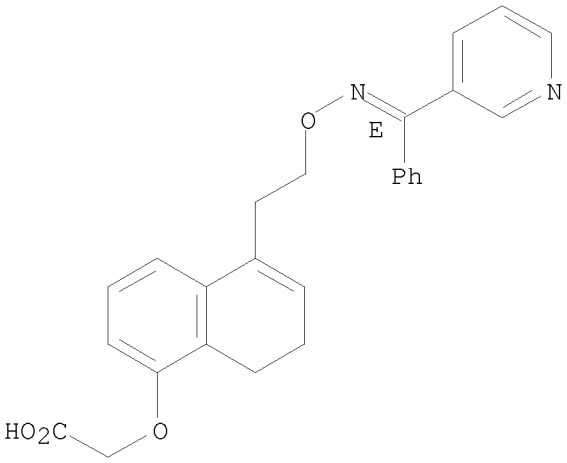
receptor agonist) on ICAM-1, B7.2, and CD40 expression mimicked that of PGE1. Moreover, PGE1 inhibited the production of IL-12 and interferon-γ in PBMC in the presence and absence of IL-18, whereas PGE1 induced IL-10 production In conclusion, IP receptor and EP2/EP4 receptor play an important role in the action of PGE1 on the expression of adhesion mols. on monocytes and cytokine production

IT 176391-41-6, ONO-1301
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IP receptor agonist; PGE1 effect on adhesion mol. expression and cytokine production in human peripheral blood mononuclear cells and involved receptor mechanisms)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 139:211404 CA

TITLE: Characterization of the transport properties of organic anion transporting polypeptide 1 (oatp 1) and Na+/taurocholate cotransporting polypeptide (Ntcp): comparative studies on the inhibitory effect of their possible substrates in hepatocytes and cDNA-transfected COS-7 cells. [Erratum to document cited in CA132:220179]

AUTHOR(S): Kouzuki, Hirokazu; Suzuki, Hiroshi; Stieger, Bruno; Meier, Peter J.; Sugiyama, Yuichi

CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 302(2), 835
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

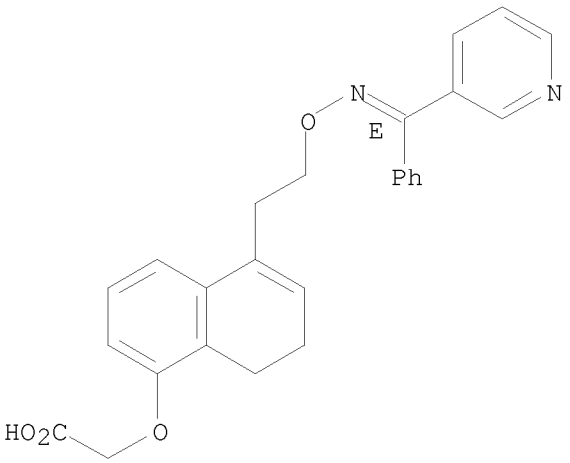
AB In Discussion, the last sentence of the first paragraph stated that "the results of the present study are in good agreement with the previous reports, although we have no good reason to account for the discrepancy in the inhibitory nature of deosycholate between the previous study [Platte HD, Honscha W, Schuh K, and Petzinger E (1966) Eur J Cell Biol 70:54-60] and the present one (Figs. 1 and 3).". This statement is not justified, however, because Platte et al. (1996) did not use deoxycholate. In their inhibition studies, Platte et al. (1996) found the ranking of bile acids is taurochenodeoxycholate > chenodeoxycholate > ursodeoxycholate ≤ cholate, which is absolutely identical to the results in Figures 1 and 3. Therefore, any discrepancy to this issue does not exist.

IT 176391-41-6, ONO-1301
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(inhibitory effects of organic anions on transport properties of organic anion transporting polypeptide 1 (oatp 1) and Na+/taurocholate cotransporting polypeptide (Ntcp)in hepatocytes and cDNA-transfected COS-7 cells (Erratum))

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



L5 ANSWER 12 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 138:378553 CA

TITLE: Pharmacophore definition and three-dimensional quantitative structure-activity relationship study on structurally diverse prostacyclin receptor agonists

AUTHOR(S): Stoll, Friederike; Liesener, Sven; Hohlfeld, Thomas; Schror, Karsten; Fuchs, Philip L.; Holtje, Hans-Dieter

CORPORATE SOURCE: Institut fur Pharmazeutische Chemie, Heinrich-Heine-Universitat Dusseldorf, Germany

SOURCE: Molecular Pharmacology (2002), 62(5), 1103-1111
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal
LANGUAGE: English

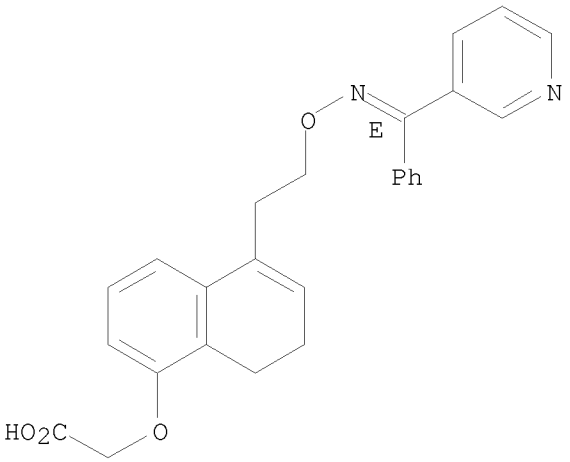
AB Prostacyclin is an endogenous mediator that shows potent platelet inhibitory activity and powerful relaxation of peripheral resistance vessels. Prostacyclin receptor agonists are valuable drugs in the treatment of various vascular diseases spanning primary pulmonary hypertension to Raynaud's syndrome. Although agonists from various structural classes were synthesized, a common pharmacophore was never defined. Therefore, an attempt was made to integrate the different agonists into a single model. A dataset of structurally diverse prostacyclin receptor agonists was tested for its affinity to the human platelet prostacyclin receptor. The dataset included prostanoid and nonprostanoid ligands comprising iloprost, cicaprost, and BMY45778. Extensive conformational analyses were performed for both classes of compds. because of the absence of rigid templates. The search and superimposition procedure yielded a pharmacophore that aligns the essential carboxylate group of the agonists as well as demonstrates that different functional groups in prostanoid and nonprostanoid agonists can be arranged in a uniform conformation. A three-dimensional quant. structure-activity relationship study was performed using the programs GRID and GOLPE. This anal. yielded a cross-validated correlation coefficient of 0.77. With this model, it is possible to predict the affinity of untested compds.

IT 176391-41-6, ONO-1301
RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study)
(pharmacophore definition and three-dimensional quant. structure-activity relationship study on structurally diverse prostacyclin receptor agonists)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 24 CA COPYRIGHT 2008 ACS on STN

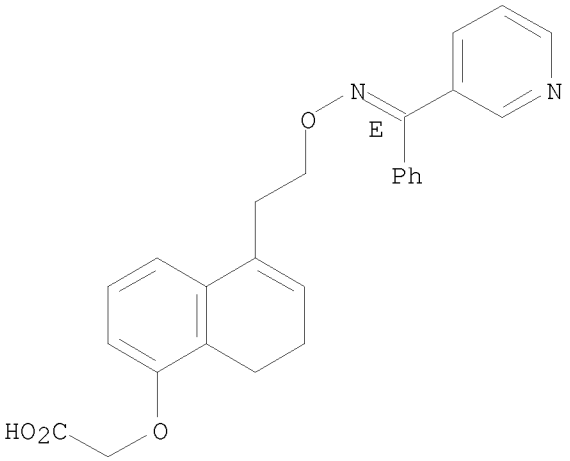
ACCESSION NUMBER: 133:247604 CA
TITLE: Protective effect of prostaglandins on the methotrexate induced damage of small intestine in rats
AUTHOR(S): Gao, Feng; Horie, Toshiharu
CORPORATE SOURCE: Laboratory of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Chiba University, Chiba, 263-8522, Japan
SOURCE: In Vivo (2000), 14(3), 453-456
CODEN: IVIVE4; ISSN: 0258-851X
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Methotrexate (MTX) treatment causes the damage of the small intestine, resulting in malabsorption. The aim of this study was to investigate the effect of prostaglandins (PGs), prostaglandin E1 (PGE1) and prostaglandin I2 (PGI2) analogs, on the MTX-induced damage of rat small intestine by examining the permeability of the small intestinal epithelium. The rats were treated as follows: MTX (15 mg/kg/day), MTX and PGE1 / PGI2 analogs (0.5 and 5 μg/kg/twice a day), PGE1 / PGI2 analogs alone, and sterile saline (control). All drugs were given orally for 5 days. The intestinal permeability of fluorescein isothiocyanate labeled dextran with average mol. mass 4.4KDa (FD-4) was examined to evaluate the dysfunction of the small intestine by the in vitro everted small intestine technique. The permeation clearance of FD-4 obtained from the in vitro experiment of the MTX-treated rats increased remarkably, but that of the MTX and PGE1 / PGI2 analog-treated rats was significantly lower than that of the MTX-treated rats. These results indicated that PGE1 or PGI2 analogs possibly alleviated the MTX-induced damage of the small intestine of rats.

IT 176391-41-6, ONO-1301
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostaglandins protective effect on methotrexate induced damage of small intestine in rat)

RN 176391-41-6 CA
CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.

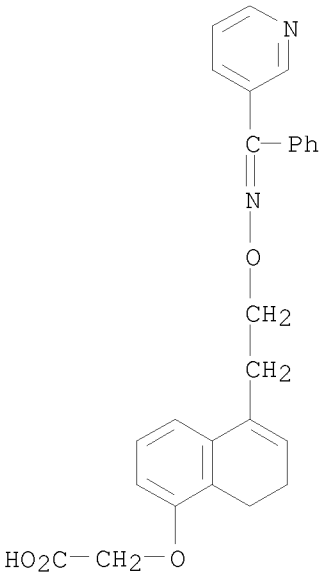


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 133:212887 CA
TITLE: Hair growth stimulants containing PGI2 agonists having no prostanoic acid structure
INVENTOR(S): Naka, Taichi; Shimomura, Takeshi
PATENT ASSIGNEE(S): Mitsubishi Chemical Corp., Japan; Ono Pharmaceutical Co.
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000239188	A	20000905	JP 1999-362118	19991221
PRIORITY APPLN. INFO.:			JP 1998-364114 A	19981222
OTHER SOURCE(S):	MARPAT 133:212887			

AB The hair growth stimulants are claimed. A composition containing [5-[2-[1-phenyl-1-(3-pyridyl)methylideneaminooxy]ethyl]-7,8-dihydronaphthalen-1-yloxy]acetic acid, EtOH, and phosphate buffer significantly promoted regrowth of mice.
IT 290355-39-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(hair growth stimulants containing PGI2 agonists having no prostanoic acid structure)
RN 290355-39-4 CA
CN Acetic acid, [[7,8-dihydro-5-[2-[[(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (9CI) (CA INDEX NAME)



L5 ANSWER 15 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 132:274709 CA
TITLE: Non-prostanoid prostacyclin mimetics as neuronal stimulants in the rat: comparison of vagus nerve and NANC innervation of the colon
AUTHOR(S): Rudd, John A.; Qian, Yue-Ming; Tsui, Kenneth K. C.; Jones, Robert L.
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, Peop. Rep. China
SOURCE: British Journal of Pharmacology (2000), 129(4), 782-790
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

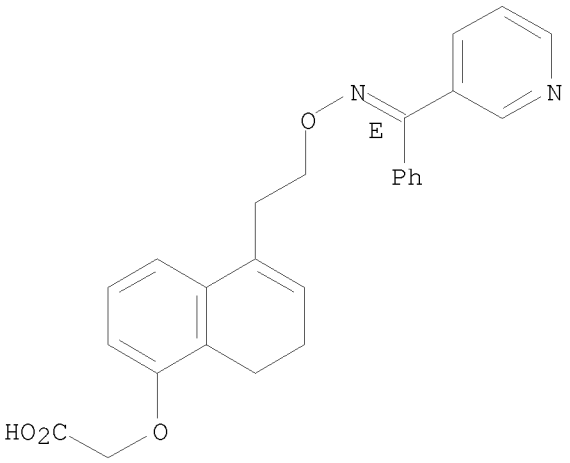
AB The spontaneous activity of the rat isolated colon is suppressed by prostacyclin analogs such as cicaprost (IC50 = 4.0 nM). Activation of prostanoid IP1-receptors located on NANC inhibitory neurons is involved. However, several non-prostanoids, which show medium to high IP1 agonist potency on platelet and vascular prepns., exhibit very weak inhibitory activity on the colon. The aim of the study was to investigate this discrepancy. Firstly, the authors have demonstrated the very high depolarizing potency of cicaprost on the rat isolated vagus nerve (EC50 = 0.23 nM). Iloprost, taprostene and carbacyclin were 7.9, 66, and 81-fold less potent than cicaprost, indicating the presence of IP1 as opposed to IP2-receptors. Three non-prostanoid prostacyclin mimetics, BMY 45778, BMY 42393 and ONO-1301, although much less potent than cicaprost (195, 990 and 1660-fold resp.), behaved as full agonists on the vagus nerve. On re-investigating the rat colon, the authors found that BMY 45778 (0.1-3 μM), BMY 42393 (3 μM) and ONO-1301 (3 μM) behaved as specific IP1 partial agonists, but their actions required 30-60 min to reach steady-state and only slowly reversed on washing. This profile contrasted

sharply with the rapid and readily reversible contractions elicited by a related non-prostanoid ONO-AP-324, which is an EP3-receptor agonist. The full vs. partial agonism of the non-prostanoid prostacyclin mimetics may be explained by the markedly different IP1 agonist sensitivities of the two rat neuronal prepns. However, the slow kinetics of the non-prostanoids on the NANC system of the colon remain unexplained, and must be taken into account when characterizing neuronal IP-receptors.

IT 176391-41-6, ONO-1301
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(prostacyclin analogs vs. non-prostanoid prostacyclin mimetics effects on vagus nerve and NANC innervation of rat colon)

RN 176391-41-6 CA
CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 132:227436 CA
TITLE: Preventive and therapeutic agents for treatment of allodynia
INVENTOR(S): Minami, Toshiaki; Ito, Seiji; Maruyama, Takayuki
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000086517	A	20000328	JP 1998-261364	19980916
PRIORITY APPLN. INFO.:			JP 1998-261364	19980916

OTHER SOURCE(S): MARPAT 132:227436

GI For diagram(s), see printed CA Issue.

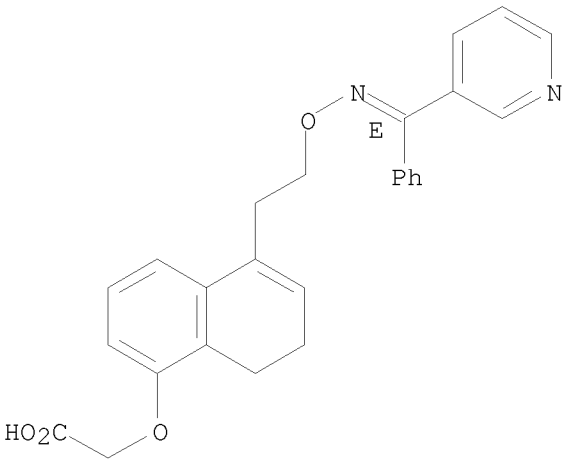
AB The agents contain cyclic compds. I [the ring D is composed of (CH2)e or CH:CH(CH2)e along with the 2 C atoms of the benzene ring; B = (CH2)p, CH:CH(CH2)q, :CH(CH2)s; e = 3-5; p = 0-4; q = 0-2; s = 0-3; R1 = H, C1-4 alkyl; R2 = ONHCHR3R4, ON:CR3R4, CHR5NHOR6, CR5:NOR6, CHR5OR6; R3 = H, (un)substituted alkyl, (un)substituted Ph, (un)substituted heterocyclyl, etc.; R4 = (un)substituted alkyl, Ph, cycloalkyl, heterocyclyl; R5 = H, C1-6 alkyl, Ph; R6 = (un)substituted alkyl, (un)substituted condensed tricyclic group] or their nontoxic salts as active ingredients. Intraspinal or oral injection of (E)-[5-[2-[1-phenyl-1-(3-pyridyl)methylideneaminooxy]ethyl]-7,8-dihydronaphthalen-1-yloxy]acetic acid significantly suppressed PGF2α-induced allodynia in mice.

IT 176391-41-6
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic compds. for treatment of allodynia)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



L5 ANSWER 17 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 132:220179 CA

TITLE: Characterization of the transport properties of organic anion transporting polypeptide 1 (oatp 1) and Na+/taurocholate cotransporting polypeptide (Ntcp): comparative studies on the inhibitory effect of their possible substrates in hepatocytes and cDNA-transfected COS-7 cells

AUTHOR(S): Kouzuki, Hirokazu; Suzuki, Hiroshi; Stieger, Bruno; Meier, Peter J.; Sugiyama, Yuichi

CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(2), 505-511
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

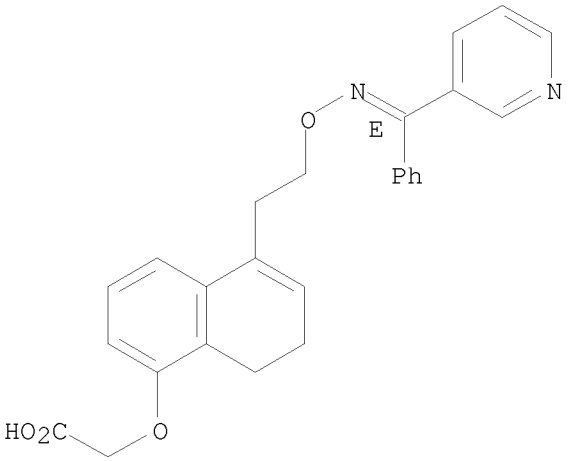
AB In the present study, we compared the inhibitory effects of organic anions (including bile acids) on the uptake of taurocholate (TC) and estradiol 17β-D-glucuronide (E217βG), typical substrates for sodium taurocholate cotransporting polypeptide (Ntcp) and organic anion transporting polypeptide (oatp 1), resp., using primary cultured rat hepatocytes and Ntcp- or oatp1-transfected COS-7 cells. The Na+-dependent uptake of TC was inhibited by nine bile acids and five nonbile acid organic anions in a concentration-dependent manner, and their inhibitory effects were similar in both primary cultured rat hepatocytes and Ntcp-transfected COS-7 cells. BQ-123 (1 μM) and indomethacin (10 μM), both of which exhibit no Ntcp-mediated transport, significantly inhibited the Na+-dependent uptake of TC mediated by Ntcp. In addition, the Na+-independent uptake of E217βG was inhibited by 15 organic anions in a concentration-dependent manner, and their inhibitory effects were similar between primary cultured rat hepatocytes and oatp 1-transfected COS-7 cells. BQ-123 (1 μM), pravastatin (1 μM), and indomethacin (10 μM), all of which do not undergo oatp 1-mediated transport, significantly inhibited the Na+-independent uptake of E217βG mediated by oatp 1. These results are consistent with the hypothesis that the hepatic uptake of TC and E217βG is predominantly mediated by Ntcp and oatp 1, resp. In addition, it was clearly demonstrated that we cannot refer to the substrate specificity of transporters based on inhibition studies.

IT 176391-41-6, ONO-1301
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitory effects of organic anions on transport properties of organic anion transporting polypeptide 1 (oatp 1) and Na+/taurocholate cotransporting polypeptide (Ntcp)in hepatocytes and cDNA-transfected COS-7 cells)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

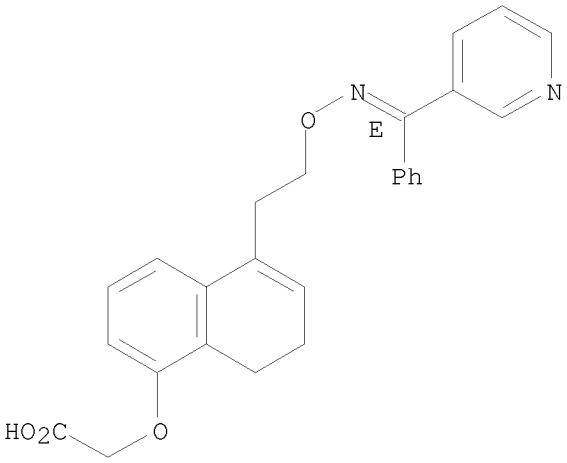
L5 ANSWER 18 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 128:289679 CA
TITLE: Kinetic study of the hepatobiliary transport of a new prostaglandin receptor agonist
AUTHOR(S): Imawaka, Haruo; Sugiyama, Yuichi
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo, 113, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 284(3), 949-957
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacokinetics of the hepatobiliary transport of an anionic drug, 7,8-dihydro-5-[(E)-[[a-(3-pyridyl)-benzylidene]aminooxy]ethyl]-1-naphthyloxyacetic acid (ONO-1301), a new prostaglandin (PG) I2 receptor agonist, was investigated in rats. During i.v. infusion of this compound, the drug concns. in arterial blood, hepatic vein and liver and the biliary excretion rate were measured at steady state. At a low infusion rate, 30% of the ONO-1301 was extracted by the liver during a single pass, and the main clearance organ was demonstrated to be the liver. The total clearance, Cltot; hepatic extraction ratio, EH; and liver-to-plasma concentration ratio, Kp values, decreased as the infusion rate increased. Considering the infusion rate-dependent decrease in all three parameters, saturation of hepatic uptake was suggested to be the cause of the nonlinear pharmacokinetics. To confirm this hypothesis, the time profiles of the plasma and liver concns. of ONO-1301 after i.v. administration of various doses (0.01-25 mg/kg) were analyzed in vivo. The early-phase hepatic uptake clearance at lower doses (0.01-1 mg/kg) was 28 mL/min/kg, which is close to the hepatic plasma flow rate. The uptake clearance also was decreased at the higher doses. The uptake mechanism was investigated with isolated rat hepatocytes. Both Na+-dependent and -independent uptake were observed and these were inhibited by hypothermia and ATP depletors, which suggests that the uptake is via carrier-mediated active transport. The initial uptake velocity exhibited concentration dependence, and the kinetic parameters were as follows: Km, 15.6 μM (Na+-dependent) and 3.8 μM (Na+-independent); Vmax, 5.9 nmol/min/mg (Na+-dependent) and 4.8 nmol/min/mg (Na+-independent). With these in vitro transport parameters, the plasma unbound fraction and the hepatic plasma flow rate, the hepatic uptake clearance was calculated from a math. model. The calcn. also indicated that the uptake was so rapid that it was limited by the plasma flow rate. It is concluded that the carrier-mediated active transport systems demonstrated in vitro are responsible for the nonlinear pharmacokinetics of ONO-1301.

IT 176391-41-6, ONO 1301
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(kinetic study of the hepatobiliary transport of a new prostaglandin receptor agonist)

RN 176391-41-6 CA
CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 127:315085 CA
TITLE: Ligand binding specificities of the eight types and subtypes of the mouse prostanoid receptors expressed in Chinese hamster ovary cells
AUTHOR(S): Kiriyama, Michitaka; Ushikubi, Fumitaka; Kobayashi, Takuya; Hirata, Masakazu; Sugimoto, Yukihiko; Narumiya, Shuh
CORPORATE SOURCE: Department of Pharmacology, Kyoto University Faculty of Medicine, Kyoto, 606, Japan
SOURCE: British Journal of Pharmacology (1997), 122(2), 217-224
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Eight types and subtypes of the mouse prostanoid receptor, the prostaglandin D (DP) receptor, the prostaglandin F (FP) receptor, the prostaglandin I (IP) receptor, the thromboxane A (TP) receptor and the EP1, EP2, EP3 and EP4 subtypes of the prostaglandin E receptor, were stably expressed in Chinese hamster ovary cells. Their ligand binding characteristics were examined with thirty two prostanoids and their analogs by determining the Ki values from the displacement curves of radioligand binding to the resp. receptors. The DP, IP and TP receptors showed high ligand binding specificity and only bound their own putative ligands with high affinity such as PGD2, BW 245C and BW 868C for DP, cicaprost, iloprost and isocarbacyclin for IP, and S-145, I-BOP and GR 32191 for TP. The FP receptor bound PGF2α and fluprostenol with Ki values of 3-4 nM. In addition, PGD2, 17-phenyl-PGE2, STA2, I-BOP, PGE2 and M&B-28767 bound to this receptor with Ki values less than 100 nM. The EP1 receptor bound 17-phenyl-PGE2, sulprostone and iloprost in addition to PGE2 and PGE1, with Ki values of 120 nM. The EP2 and EP4 receptors showed similar binding

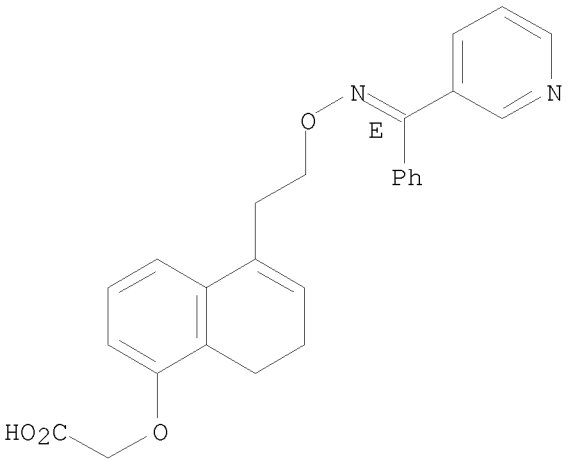
profiles. They bound 16,16-dimethyl PGE2 and 11-deoxy-PGE1 in addition to PGE2 and PGE1. The two receptors were discriminated by butaprost, AH-13205 and AH-6809 that bound to the EP2 receptor but not to the EP4 receptor, and by 1-OH-PGE1 that bound to the EP4 but not to the EP2 receptor. The EP3 receptor showed the broadest binding profile, and bound sulprostone, M&B-28767, GR 63799X, 11-deoxy-PGE1, 16,16-dimethyl-PGE2 and 17-phenyl-PGE2, in addition to PGE2 and PGE1, with Ki values of 0.6-3.7 nM. In addition, three IP ligands, iloprost, carbacyclin and isocarbacyclin, and one TP ligand, STA2, bound to this receptor with Ki values comparable to the Ki values of these compds. for the IP and TP receptors, resp. 8-Epi-PGF2α showed only weak binding to the IP, TP, FP, EP2 and EP3 receptor at 10 μM concentration

IT 176391-41-6, ONO 1301
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mouse prostanoid receptor type ligand binding specificities after expression in Chinese hamster ovary cells)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 126:181065 CA

TITLE: Modulation of anti-glomerular basement membrane nephritis in rats by ONO-1301, a non-prostanoid prostaglandin I2 mimetic compound with inhibitory activity against thromboxane A2 synthase

AUTHOR(S): Hayashi, Kazumi; Nagamatsu, Tadashi; Oka, Tatsuya; Suzuki, Yoshio

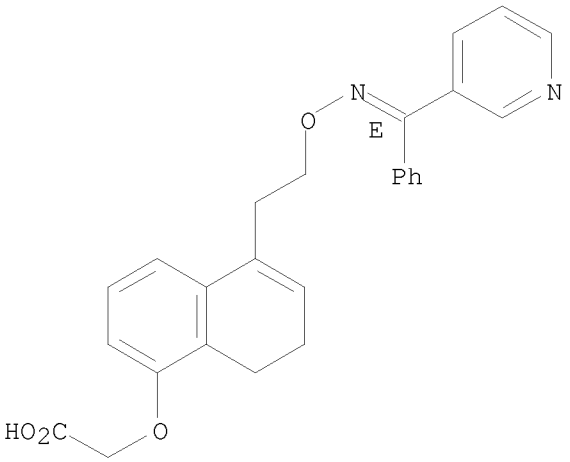
CORPORATE SOURCE: Department of Pharmacology, Faculty of Pharmacy, Meijo University, Nagoya, 468, Japan

SOURCE: Japanese Journal of Pharmacology (1997), 73(1), 73-82
CODEN: JJPAAZ; ISSN: 0021-5198

PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antinephritic effects of ONO-1301 ([7,8-dihydro-5-[(E)-[[a-(3-pyridyl)benzylidene]-aminooxy]ethyl]-1-naphthyloxy]acetic acid) on crescentic-type anti-glomerular basement membrane (GBM) nephritis in rats were investigated. ONO-1301 was orally given to crescentic-type anti-GBM nephritic rats for 40 days after the induction of nephritis. ONO-1301 (30 mg/kg) suppressed the elevation of protein excretion into urine. In the ONO-1301-treated rats, cholesterol and urea nitrogen content in the plasma was lower than that of the nephritic control rats. Histol. observation demonstrated that ONO-1301 suppressed the incidence of crescent formation and adhesion of capillary wall to Bowman's capsule. However, ONO-1301 failed to inhibit the antibody production against rabbit IgG and the rat-IgG deposition on the GBM. The increase in very late antigen-4 (CD49b, VLA-4)-pos. cells in nephritic glomeruli was significantly reduced by ONO-1301 treatment on day 5. CAMP-elevating agents inhibited the up-regulation of vascular cell adhesion mol.-1 (VCAM-1) expression on the surface of human umbilical vein endothelial cells (HUVECs) mediated by tumor necrosis factor (TNF)-α. These findings suggest that the antinephritic action of ONO-1301 is due to, at least in part, inhibition of intraglomerular accumulation of leukocytes through the prevention of the up-regulation of VCAM-1.
IT 176391-41-6, ONO-1301
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulation of anti-glomerular basement membrane nephritis by ONO-1301)
RN 176391-41-6 CA
CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.

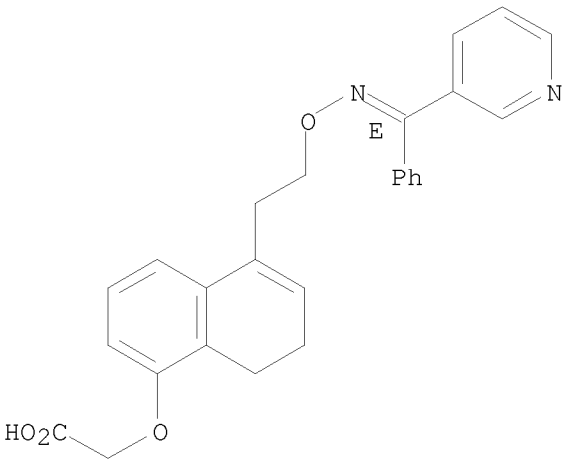


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 126:69709 CA
TITLE: Hepatic uptake mechanism of the prostaglandin I2

receptor agonist ONO 1301
AUTHOR(S): Imawaka, Haruo; Hirohashi, Tomoko; Suzuki, Hiroshi; Sugiyama, Yuichi
CORPORATE SOURCE: Dep. PHarmaceutics, Univ. Tokyo, Tokyo, Japan
SOURCE: Yakuri to Chiryo (1996), 24(Suppl. 12), S/2063-S/2069
CODEN: YACHDS; ISSN: 0386-3603
PUBLISHER: Raifu Saiensu Shuppan K.K.
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Hepatic uptake mechanism of the prostaglandin I receptor agonist ONO 1301 was studied in isolated rat liver cells and frog oocytes. The results indicated that ONO 1301 is transported by Na+-dependent and -nondependent mechanisms, with Na+-dependent taurocholate transporter and organic anion transporter, resp., as the carriers.
IT 176391-41-6, ONO 1301
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hepatic uptake mechanism of the prostaglandin I2 receptor agonist ONO 1301)
RN 176391-41-6 CA
CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



L5 ANSWER 22 OF 24 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 124:306475 CA
TITLE: Kinetic study for hepatobiliary transport of a novel prostaglandin I2 receptor agonist, ONO-1301
AUTHOR(S): Imawaka, Haruo; Sugiyama, Yuichi
CORPORATE SOURCE: Fac. Pharmaceutical Sci., Univ. Tokyo, Japan
SOURCE: Yakuri to Chiryo (1996), 24(Suppl. 1), 171-7
CODEN: YACHDS; ISSN: 0386-3603
PUBLISHER: Raifu Saiensu Shuppan K.K.
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The kinetics of hepatobiliary transport of a novel prostaglandin I receptor agonist, ONO-1301, were studied in normal and EHBR (hereditary

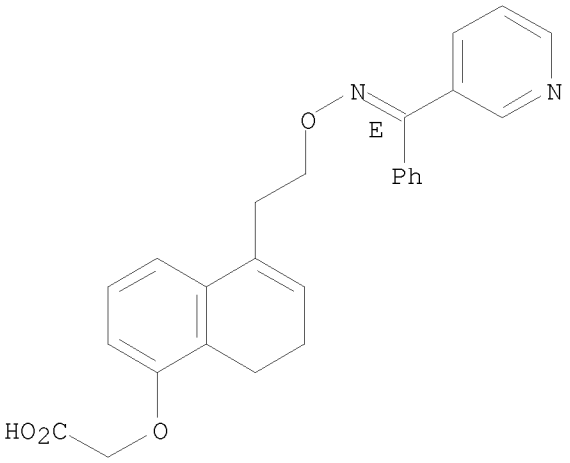
chronic conjugated hyperbilirubinemia) rats following i.v. injection. ONO-1301 was taken up by the liver and excreted with its water-soluble metabolite into the bile. The results indicated that the hepatobiliary transport is carrier mediated, and multi-specific organic anion transporter is involve in the excretion of the metabolite, but not of the parent compound

IT 176391-41-6, ONO 1301
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(kinetic study for hepatobiliary transport of a novel prostaglandin I2 receptor agonist, ONO-1301)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



L5 ANSWER 23 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 122:204789 CA

TITLE: ONO-AP-500-02: A non prostanoid prostaglandin I2 mimetic with inhibitory activity against thromboxane synthase

AUTHOR(S): Kondo, Kigen; Machii, Koji; Narita, Masami; Kawamoto, Akihiko; Yamasaki, Shinichi; Hamanaka, Nobuyuki

CORPORATE SOURCE: Minase Research Institute, Ono Pharmaceutical Co., Ltd., Mishima, 618, Japan

SOURCE: Advances in Prostaglandin, Thromboxane, and Leukotriene Research (1995), 23(Prostaglandins and Related Compounds), 401-3
CODEN: ATLRD6; ISSN: 0732-8141

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The biochem. and pharmacol. properties of ONO-AP-500-02 were studied. ONO-AP-500-02 bound to human platelet IP receptor but not to guinea pig ileum EP receptors, TP receptors of human platelet, or FP receptors of rat ovary. ONO-AP-500-02 inhibited human platelet aggregation at lower doses than that of dog or rabbit platelets. It also inhibited human platelet thromboxane synthase activity. Intraduodenal ONO-AP-500-02 inhibited

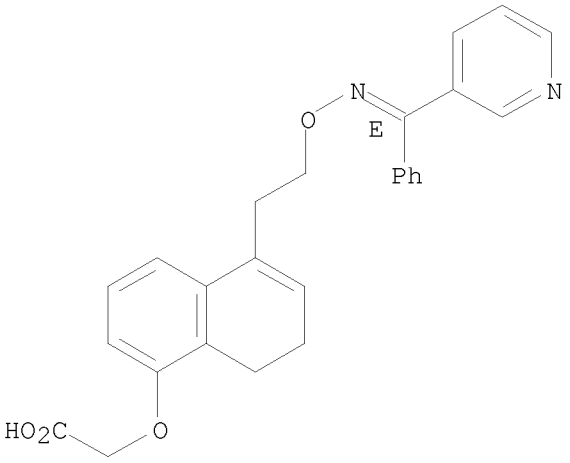
platelet aggregation and TXB2 formation by 50% at similar concns.

IT 176391-41-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ONO-AP-500-02 as PGI2 mimetic with inhibitory activity against thromboxane synthase)

RN 176391-41-6 CA

CN Acetic acid, 2-[[7,8-dihydro-5-[2-[[(E)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.



L5 ANSWER 24 OF 24 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 120:217011 CA

TITLE: Preparation of [(aminooxy)alkyl]naphthalenyloxyacetates

INVENTOR(S): Hamanaka, Nobuyuki; Takahashi, Kanji; Tokumoto, Hidekado

PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

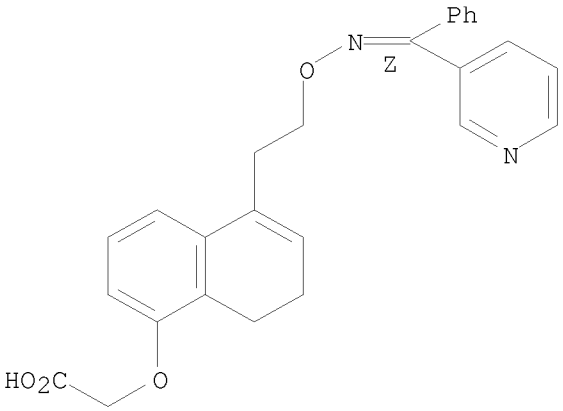
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 581187	A1	19940202	EP 1993-111689	19930721
EP 581187	B1	19961204		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2100918	A1	19940122	CA 1993-2100918	19930720
CA 2100918	C	19970121		
JP 06087811	A	19940329	JP 1993-200345	19930720
KR 191137	B1	19990615	KR 1993-13623	19930720
AT 145892	T	19961215	AT 1993-111689	19930721
ES 2097402	T3	19970401	ES 1993-111689	19930721

US 5480998	A	19960102	US 1994-215019	19940317
JP 08109162	A	19960430	JP 1995-264666	19950920
JP 2649507	B2	19970903		

PRIORITY APPLN. INFO.: JP 1992-215457 A 19920721
US 1993-93614 B1 19930720

OTHER SOURCE(S): MARPAT 120:217011
GI For diagram(s), see printed CA Issue.
AB Title compds. I (the ring represented by DB + Q, Q1, Q2, Q3; R1 = H, (substituted) C1-4 alkyl; R2 = H, C1-8 alkyl, Ph, C4-7 cycloalkyl, 4-7-membered heterocyclyl, etc., with provisos) and salts thereof, possessing agonistic activity on PGI2 receptor, are prepared Phenyl-(2-pyridylmethylene)hydroxyamine was added to NaH in DMF followed by Me [5-(2-bromoethyl)-5,6,7,8-tetrahydronaphthalen-1-oxy]acetate in DMF to give Me [5-[2-[1-phenyl-1-(3-pyridyl)methyleneaminooxy]ethyl]-5,6,7,8-tetrahydronaphthalen-1-yloxy]acetate which was reacted with NaOH in THF-MeOH to give the free acid (II). In test for agonistic activity on PGI2 receptor, the inhibitory activity on binding of [3H]-iloprost to GGI2 receptor on human blood platelet membrane fraction for II was IC50 0.33 μM. Pharmaceutical formulations comprising I are given.
IT 153814-74-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of as PGI2 agonist)
RN 153814-74-5 CA
CN Acetic acid, [[7,8-dihydro-5-[2-[[(Z)-(phenyl-3-pyridinylmethylene)amino]oxy]ethyl]-1-naphthalenyl]oxy]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



=> d his

(FILE 'HOME' ENTERED AT 10:23:13 ON 14 APR 2008)

FILE 'REGISTRY' ENTERED AT 10:23:43 ON 14 APR 2008
L1 STRUCTURE UPLOADED
L2 0 S L1 SAM
L3 4 S L1 FULL

FILE 'CA' ENTERED AT 10:24:10 ON 14 APR 2008

```
L4             0 S L2
L5            24 S L3

=>

---Logging off of STN---



=>
Executing the logoff script...


=> LOG Y

STN INTERNATIONAL LOGOFF AT 10:24:42 ON 14 APR 2008
```